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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/435,257	11/05/1999	PAUL A. CLEMONS	APBI-PO1-385	4970

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EXAMINER	
MONTANARI, DAVID A	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/435,257	CLEMONS ET AL.	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 8/03/05.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-18,20-37 and 51 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-18, 20-37, and 51 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants arguments and amendments filed on August 3rd, 2005 have been entered.

2. Claims 1, 12, and 26-27 have been amended.

3. Claims 19, and 38-50 have been canceled.

4. Rejection of claims 1-18, 20-31, and 32-37 under 35 U.S.C. 101, double patenting has been withdrawn.

5. Rejection of claims 1-6, 20-21, 26, 34, and 36 under 35 U.S.C. 102(b), has been withdrawn.

6. Claims 1-18, 20-37, and 51 are examined in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-33 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons set forth in the office action mailed March 1st, 2005. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record mailed March 1st, 2005.

Claims 32-33 are drawn to a non-human animal containing host cells comprising and expressing a recombinant nucleic acid.

Applicants arguments in amendment filed August 3rd, 2005 have been fully considered but are not persuasive.

Applicants argue in amendment that today and of the filing date of the instant application the making of transgenic animals was sufficiently routine and well known in the art to moot the Examiner's concerns. Applicants continue to argue that the correlated expression of a transgene with induction of a disease state is not the most relevant use of a CAB domain, but more so for the study of a drug-binding domain in vivo for use of a component of a ligand-regulated switch mechanism. Applicants present art by Kistner, St-Onge, and Furth to support the claimed invention for use in animal models of biological switches, and present further art by Soldevila, Mallet, Freeman, and Kazansky for the generation of transgenic animals. The applicant continues to argue that the Examiner has taken a few phrases from references published significantly prior to the filing of the instant application. These arguments are not persuasive. Applicants state that the claimed transgenic non-human animals are models of biological switches, however there is no such recitation in the claims. Further with regard to antiquated art teaching the unpredictability of generating transgenic animals, the Examiner would like to present recent art supporting the Examiners original position filed in the Office Action dated March 1, 2005. The art teaches that transgenic mouse lines are generated by microinjection of the linear DNA of interest into the nucleus of an oocyte or transfected into embryonic stem (ES) cells, which then randomly integrates into the genome (Ristevski, Molecular Biotechnology, Vol. 29, 2005, pg. 159 col. 1 parag. 2 lines 1-5). Currently only mouse ES cells have been established that result in

a transgenic animal (Smith, 2002, J. of Biotechnology, Vol. 99, pg. 3 col. 1, parag. 4 lines 1-3). With regard to transgene integration the art teaches that the site of integration is uncontrolled and yet is critical due to the possibility of integration into a silent locus. Random integration may occur, resulting in the insertional inactivation (insertional mutagenesis) of a gene at the site of integration, resulting in a loss of function that may be mistakenly attributed to over expression of the transgene (Ristevski, pg. 159 col. 1 parag. 2 lines 5-14). Further, insertional mutagenesis of a gene may not be immediately apparent if a recessive gene has been inactivated, as phenotypic abnormalities will not be evident until homozygous transgenic lines have been established (Ristevski, pg. 159 col. 1 parag. 2 lines 14-19). The site of integration may also result in altered tissue specificity, although the promoter used behaves differently at its normal chromosomal localization, with neighboring regulatory elements potentially influencing the transcriptional activity of the transgene (Ristevski, pg. 159 col. 1 parag. 3 lines 1-7). This is known as chromosomal position effects, where host sequences surrounding the site of transgene integration can alter the expected expression pattern, turning it ectopic or not detectable (Montoliu, 2002, Cloning and Stem Cells, Vol. 4, pg 39, col. 1). With regard to copy number the art teaches that controlling the transgene copy number (usually integration is a singular event with multiple copies integrated in tandem) is also problematic in the generation of transgenic animals (Ristevski, pg. 159 col. 1 parag. 3 lines 7-11). A high tandem copy number results in a gene silencing effect, and further, is undesirable if the effect of a gene dosage is being addressed, as multiple copies will not recapitulate relevant levels of expression (Ristevski, pg. 159 col. 1 parag. 3 lines 11-14 bridge col. 2 parag. 1). With regard to transgene expression, the art teaches bluntly that, "many transgenes work poorly" (Houdebine, 2002, J. of Biotechnology, Vol. 98, pg.

150, col. 1 parag. 4 line 1). Transgene expression is often very low or not specific of the promoter added in the gene construct, and are generally attributed to position effects in chromatin as discussed above (Houdebine, pg. 150, col. 1 parag. 4 lines 1-5). The art continues to teach that a transgene is generally poorly expressed when it contains a cDNA rather than the corresponding genomic DNA sequence with its introns, has multiple copies integrated in the same site, and when a bacterial gene is used (Houdebine, pg. 150 col. 2 lines 4-9). Overexpression of a transgene of interest also has inherent problems. This is often the case when the overproduced protein shares only a part of the properties of an endogenous protein, which can result in inhibition of the endogenous protein, by the transgene of interest working in a transdominant negative manner (Houdebine, pg. 152, col. 2 parag. 4). The art continues that the generation of transgenic animals routinely involves one of two methods of exogenous DNA delivery to the recipient cells, retroviral infection or microinjection (Smith, pgs. 5-11). However, each method possesses significant unpredictability for the skilled artisan to implement. Retroviral vectors result in inconsistency and irreproducibility of transgene expression due to random integration with host DNA (Smith, pg. 6, col. 1 parag. 2), and instability due to the integrated retroviral DNA possessing the ability to spontaneously reactivate (Smith, pg. 6, col. 1 parag. 5). Microinjection of recipient cells with exogenous DNA presents the problem of mosaicism to the skilled artisan. The majority (≈ 85%) of pronuclear microinjection-derived transgenic founders are mosaics of transgenic and non-transgenic cells (Smith, pg. 7, col. 2 parag. 2 lines 1-4). This becomes problematic since transmission of the transgene is dependent upon the existence and extent of germline colonization by transgene-containing cells, so that when transmission does occur, the transgene is inherited in a mendelian fashion resulting in only

a small portion of the transgene being passed onto offspring (Smith, pg. 7, col. 2 parag. 3, bridge pg. 8 col. 1 lines 1-8). Significant restraints also exist for the skilled artisan attempting microinjection of other animal species other than mouse. Cow, pig, and sheep eggs are optically opaque, unlike mice, which makes microinjection of the targeted pronuclei extremely difficult (Smith, pg. 11 col. 2 parag. 1). In view of the recent art summarized above, the skilled artisan at the time of filing would surmise that the field of transgenesis is still very unpredictable.

Thus while the CAB transgenic non-human animals are not a disease model, the claimed invention is drawn to any transgenic non-human animal. The art provided by the applicant in support of the claimed invention as stated above is all drawn to the generation of transgenic mice. All transgenic non-human animals encompasses many animals of different species that vary enormously, and the instant specification has provided no guidance to the skilled artisan with regard to the creation of a CAB-domain transgenic animal. The skilled artisan would not be able to envision or create the creation of all or any non-human transgenic animal(s) comprising a CAB-domain based on the guidance of the instant specification. Thus, because or reasons of record mailed on March 1st, 2005, and the art of record above, and significant deficits in the instant specification regarding the creation of any non-human transgenic animal the rejection is maintained.

Claims 26-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated host cell *in vitro* comprising a recombinant nucleotide sequence encoding a fusion protein comprising a portion of calcineurin A and a portion of calcineurin B, and a method for producing said host cell *in vitro*, does not reasonably provide

enablement for using isolated cells, including encapsulated cells, comprising the said recombinant nucleic acid in a cell based therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for reasons of record mailed March 1st, 2005.

Applicants arguments in amendment filed August 3rd, 2005 have been fully considered but are not persuasive.

Applicants argue in amendment the Examiner appears to base this rejection on the mistaken assumption that the sole purpose of the claimed composite constructs is to mimic or ameliorate disease symptoms and relies on relatively old references to question the enablement of the presently claimed invention. Applicant continues to argue that the specification demonstrates a variety of uses for the claimed recombinant cells and that the examples provided in the specification provide sufficient enablement that the subject constructs can be expressed in cells. However, when claims 26-31 are examined for their full breadth they encompass transgenic cells in any animal (claims 26-27), and isolated cells from any transgenic animal (claims 28-31). The issue is not whether the applicant can express the claimed recombinant nucleic acid in an isolated cell, but the host cells of claims 26-27 which encompass a transgenic cell in any animal. The claims as written would encompass the creation of a transgenic human to enable the isolation of a cell of human origin which comprises a recombinant nucleic acid. The instant specification has provided no guidance for such an embodiment. Thus for reasons of record and above the rejection is maintained. The limitation of " an isolated host cell" would render this rejection moot.

Claims 26, 27, 34, 35, 36 and 37 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated host cell *in vitro* comprising a nucleotide sequence encoding a CAB domain and methods for producing genetically engineered host cells *in vitro*, does not reasonably provide enablement for a host cell *in vivo* comprising a CAB domain protein, wherein said cell is used for cell based or in site gene therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for reasons of record mailed March 1st, 2005.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is 1-571-272-3108. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 1-571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David A. Montanari, PhD

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER